NaHCO₃ does not affect arterial O₂ tension but attenuates desaturation of hemoglobin in maximally exercising Thoroughbreds

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Manohar, Murli, Thomas E. Goetz, and Aslam S. Hassan. NaHCO₃ does not affect arterial O₂ tension but attenuates desaturation of hemoglobin in maximally exercising Thoroughbreds. J Appl Physiol 96: 1349–1356, 2004. First published December 12, 2003; 10.1152/japplphysiol.01083.2003.—The objective of the present study was to examine the effects of preexercise NaHCO₃ administration to induce metabolic alkalosis on the arterial oxygenation in racehorses performing maximal exercise. Two sets of experiments, intravenous physiological saline and NaHCO₃ (250 mg/kg iv), were carried out on 13 healthy, sound Thoroughbred horses in random order, 7 days apart. Blood-gas variables were examined at rest and during incremental exercise, leading to 120 s of galloping at 14 m/s on a 3.5% uphill grade, which elicited maximal heart rate and induced pulmonary hemorrhage in all horses in both treatments. NaHCO₃ administration caused alkalosis and hemodilution in standing horses, but arterial O₂ tension and hemoglobin-O₂ saturation were unaffected. Thus NaHCO₃ administration caused a reduction in arterial O₂ content at rest, although the arterial-to-mixed venous blood O₂ content gradient was unaffected. During maximal exercise in both treatments, arterial hypoxemia, desaturation, hypercapnia, acidosis, hyperthermia, and hemoconcentration developed. Although the extent of exercise-induced arterial hypoxemia was similar, there was an attenuation of the desaturation of arterial hemoglobin in the NaHCO₃-treated horses, which had higher arterial pH. Despite these observations, the arterial blood O₂ content of exercising horses was less in the NaHCO₃ experiments because of the hemodilution, and an attenuation of the exercise-induced expansion of the arterial-to-mixed venous blood O₂ content gradient was observed. It was concluded that preexercise NaHCO₃ administration does not affect the development and/or severity of arterial hypoxemia in Thoroughbreds performing short-term, high-intensity exercise.

exercise-induced arterial hypoxemia; blood-gas tensions; metabolic alkalosis; hemoglobin-O₂ saturation; arterial desaturation during exercise

SIMILAR TO HUMAN ATHLETES (5, 31), strenuously exercising Thoroughbred horses routinely experience arterial hypoxemia and desaturation of hemoglobin, which limit performance (19). Metabolic acidosis is also observed in strenuously exercising racehorses as blood lactate concentration increases dramatically (19). To mitigate the adverse effects of acidosis and gain a putative ergogenic effect, racehorses are frequently premedicated with NaHCO₃. However, despite considerable investigation (1, 6, 8–10, 12, 15, 17, 18, 20, 21, 33), consensus does not exist regarding the beneficial ergogenic effects of NaHCO₃ premedication in racehorses. Previous studies have largely been focused on changes in the jugular venous blood acid-base status during and postexercise (6, 8–10, 12, 17, 18, 21, 33), although muscle enzymes, substrates, and metabolites have also been studied (8, 9, 15, 33). There has been one report in Thoroughbred horses, wherein arterial blood-gas tensions were examined during strenuous exercise performed after NaHCO₃ administration (20). In this report (20), NaHCO₃ administration markedly exaggerated the exercise-induced arterial hypoxemia; mean arterial O₂ tension during exercise performed at 80 and 110% of the maximal whole body O₂ uptake (V˙O₂ max) in the NaHCO₃ experiments was 11.1 and 9.2 Torr, respectively, lower than that in the saline-treated horses (20). However, effects of an NaHCO₃-induced accentuation of the exercise-induced arterial hypoxemia on the hemoglobin-O₂ saturation were not examined. Furthermore, horses premedicated with NaHCO₃ had significantly lower arterial O₂ tension, even during exercise performed at 40 and 60% V˙O₂ max (20), which, in healthy, unmedicated Thoroughbred horses, is not attended by changes in arterial O₂ tension (19, 23–27). These observations in exercising horses premedicated with NaHCO₃ (20) are in contrast with findings in human subjects, in whom exercise-induced arterial hypoxemia is largely unaffected by preexercise administration of NaHCO₃, but the associated alkalosis helps limit the desaturation of arterial hemoglobin (28). Because an exaggeration of the exercise-induced arterial hypoxemia following NaHCO₃ administration to horses (20) may adversely affect O₂ supply and, in turn, performance (5, 19), the objective of the present study was to reevaluate the effects of preexercise NaHCO₃ administration on the arterial oxygenation in Thoroughbred horses performing short-term, high-intensity exercise.

MATERIALS AND METHODS

Horses. Experiments were carried out on 13 healthy, sound Thoroughbred horses (5 fillies, 8 geldings), 3–6 yr old, and weighing 450 ± 23 kg. They were housed in an air-conditioned building and were accustomed to being handled by people. The horses were maintained on alfalfa hay and oats with free access to water. The horses were dewormed periodically and were inoculated with tetanus toxoid and strangles vaccine. Our protocols and procedures were approved by the Institutional Animal Care and Use Committees.

Exercise training and work intensity eliciting maximal heart rate. After initial familiarization with walking, trotting, cantering, and galloping on the high-speed treadmill for 1 wk, all horses were exercise trained for 7 wk (22–27). Thereafter, separate trials were undertaken to determine the work intensity eliciting maximal heart rate and stress failure of pulmonary capillaries (39), leading to exercise-induced pulmonary hemorrhage (EIPH). Galloping at 14 m/s on a 3.5% uphill grade elicited maximal heart rate, induced EIPH in all horses (as demonstrated by the presence of fresh blood in the pulmonary arteries).

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trachea on postexercise airway endoscopic examination; Refs. 16, 22,
36), and could not be sustained for >120 s, despite vigorous humane
couragement. Thus this workload was selected for further experi-
mentation.

Experimental design and protocol. All horses were studied in the
placebo [intravenous (IV) physiological saline] and the NaHCO3
experiments, which were carried out in random order, 7 days apart. All
experimentation was carried out at an ambient temperature of 20–
21°C.

In the NaHCO3 experiments, ~5 min after completion of baseline
measurements (rest 1) on quietly standing horses, 5% NaHCO3
solution (Abbott Laboratories, Deerfield, IL) was administered at 250
mg/kg via a previously positioned catheter in the left jugular vein. For
individual horses, the volume of 5% NaHCO3 solution varied from 1,
955 to 2,492 ml. Thereafter, horses stood quietly on the treadmill for
15 min. Then blood-gas variables and plasma protein concentrations
were determined (preexercise data). In the placebo study, after com-
pletion of baseline measurements, an equivalent volume (1,955–2,492
ml) of physiological saline was administered IV, and preexercise
measurements were made at corresponding intervals in the NaHCO3
study. The sequence of placebo and NaHCO3 experiments was ran-
momized, and 7 days were allowed between treatments on every
horse.

On completion of preexercise measurements, exercise began on the
high-speed treadmill set at a 3.5% uphill grade in the following
manner. Beginning with a walk at 2 m/s for 120 s, the belt speed was
raised in increments of 1 m/s every 60 s until the speed was 6 m/s.
After the horses had trotted at 6 m/s for 60 s, speed was raised to 8 m/s
for 60 s and then to 14 m/s. On completion of 120 s of galloping at 14
m/s on a 3.5% uphill grade, the speed was decreased first to 5 m/s
(trot) for 60 s and then to 2 m/s. Horses walked at 2 m/s for 300 s
before the treadmill was stopped. In this incremental exercise proto-
col, along with continuous core temperature measurement, simulta-
neous arterial and mixed venous blood samples were obtained for
determining blood-gas variables at 55–60 s of trotting at 6 m/s; at
55–60 s of exercise at 8 m/s; at 30, 60, 90 and 120 s of maximal
exertion; and at 120 s of walk at 2 m/s. Also, plasma protein and
mixed venous blood lactate concentrations were determined at 60 s
of exercise at 8 m/s, at 120 s of maximal exertion, and at 120 s of walk
at 2 m/s.

In both treatments, using a flexible fiber-optic endoscope (Pentax
Fiberscopes, Orangeburg, NY), nasopharynx, larynx, and trachea (up
to the carina) were examined 45–50 min postexercise to detect the
occurrence of EIPH (16, 22, 36).

Experimental procedures. On the day of the study, after local
anesthesia in the 17th intercostal space, the abdominal aorta was
catherized percutaneously (23–27). Thereafter, using local infiltra-
tion of 2% lidocaine HCl, cardiac catheters (8 F) with tip manometer
(Millar Instruments, Houston, TX), fluid-filled lumen, and a ther-
mistor (Edward Laboratories, Santa Clara, CA) were advanced into
the pulmonary artery via introducers inserted into the left jugular vein.
The catheter locations were confirmed by monitoring the characteris-
tic phasic blood pressure waveforms on an oscillograph (E for M,
Lanexa, KS). These catheters permitted simultaneous sampling of the
aortic and pulmonary arterial (mixed venous) blood, as well as con-
stant monitoring of the pulmonary arterial blood (core) tempera-
ture during the experiments. After catheter placement, horses stood
quietly on the treadmill for at least 45–50 min before baseline
measurements were initiated.

Because higher osmolality of the 5% NaHCO3 solution [1,190
mosmol/kg H2O vs. that of physiological saline (308 mosmol/kg H2O)]
causes water absorption into the vascular compartment, the associated
alterations in plasma volume or hydration status were assessed by
monitoring changes in the plasma protein concentration (2, 7, 25).
Because the quantity of circulating plasma proteins is constant in
healthy animals, acute changes in plasma protein concentration are
indicative of the changes in the plasma volume or hydration status (2,
7, 25). Plasma protein concentration was determined by refractometry
(7, 25), and the %change in plasma volume was calculated as
[(PP1/PP2 – 1.0) × 100, where PP1 and PP2 are the initial and the test
plasma protein concentrations, respectively (2, 7, 25). Blood-gas
variables were determined by using a calibrated blood-gas analyzer
and CO-oximeter (ABL520, Radiometer, Copenhagen, Denmark),
and all blood-gas tensions and pH data were corrected to the simula-
taneously measured pulmonary artery blood temperature. Mixed ve-
nous blood lactate concentration was also determined (23, 25, 26), and
%O2 extraction was calculated as (arterial-to-mixed venous blood O2
content gradient/arterial O2 content) × 100.

Data analysis. The data were subjected to repeated-measures,
split-plot design analysis of variance (SAS statistical software version
8.2, SAS Institute, Cary, NC), and the treatment comparisons were
made by using the least squares significant difference method (35).
Data for the placebo as well as the NaHCO3 experiments were also
individually subjected to analysis of variance followed by Newman-
Keuls multiple-range test (35) to determine the significant effects of
work intensity and duration within each treatment. For all statistical
analyses, the level of significance was set at P < 0.05. The data are
presented as means ± SE.

RESULTS

Arterial bicarbonate concentration and pH. See Fig. 1. The
IV administration of NaHCO3 was well tolerated by the horses.
Preexercise arterial pH increased to 7.494 ± 0.004 (vs.
7.401 ± 0.003 pre-NaHCO3 administration; P < 0.0001) as
arterial bicarbonate concentration increased to 36.3 ± 0.3 mM.
Submaximal exercise in either treatment was not attended by
changes in arterial pH from respective preexercise values.
However, acidosis developed during maximal exercise in both
treatments as blood lactate concentration increased markedly
(Fig. 2). Although the extent of the net drop in arterial pH from
the beginning to the end of maximal exertion (change in pH =
0.306 ± 0.020 and 0.310 ± 0.018 in the placebo and NaHCO3
experiments, respectively) was not different between treat-
ments, the arterial pH was maintained at a higher value (P <
0.001) in the NaHCO3 experiments. At 120 s of maximal
exercise, the arterial pH values in the placebo and NaHCO3
experiments were 7.099 ± 0.028 and 7.177 ± 0.021, respect-
ively (P < 0.001).

Plasma protein and hemoglobin concentrations. See Fig. 3.
Following IV NaHCO3 administration to standing horses, plasma
protein concentration decreased (P < 0.0001) as
14.6 ± 0.6% expansion of the plasma volume occurred. Con-
comitantly, hemoglobin concentration also decreased (P <
0.01) in the NaHCO3-treated horses. Incremental exercise in
both treatments caused progressive increments in these vari-
ables; however, values observed in the NaHCO3 experiments
remained less than in the placebo study, indicating that expan-
sion of the plasma volume persisted during exertion. Plasma
volume in the NaHCO3 experiments exceeded that in the
placebo study by 12.7 ± 0.9% at 60 s of exercise at 8 m/s and
by 10.7 ± 1.4% at 120 s of maximal exercise. Arterial
hemoglobin concentration approached 22.2 ± 0.3 and 21.1 ±
0.3 g/dl at 120 s of maximal exertion in the placebo and
NaHCO3 experiments, respectively (P < 0.01).

Core temperature. See Fig. 4. The incremental exercise
protocol caused a similar, progressive rise in core temperature as
exercise duration increased in both treatments. At 120 s of
maximal exertion, core temperature had increased by 3.4 ±
and arterial O₂ tension did not change significantly (Fig. 5A). As exercise duration progressed from 30 to 120 s, arterial O₂ tension was 72.4 ± 2.0 and 69.3 ± 1.8 Torr, respectively (vs. 101.5 ± 0.8 and 99.7 ± 1.1 Torr preexercise, respectively; both P < 0.0001).

Desaturation of arterial hemoglobin was also evident at 30 s of maximal exercise in both treatments, and, as exercise duration progressed to 120 s, the desaturation of arterial hemoglobin intensified (Fig. 5B). However, arterial hemoglobin-O₂ saturation was higher (P < 0.05) in the NaHCO₃ experiments. At 120 s of maximal exercise in the placebo and the NaHCO₃ experiments, arterial hemoglobin-O₂ saturation was 84.7 ± 1.7 and 86.8 ± 1.3%, respectively.

Mixed venous blood O₂ tension and hemoglobin-O₂ saturation. See Fig. 5. Following NaHCO₃ administration, preexercise mixed venous blood O₂ tension decreased, but hemoglobin-O₂ saturation remained unaffected. The incremental exercise protocol caused work intensity-related reductions in these variables in both treatments. From our data, O₂ tension required for half-maximal saturation of the blood could not be determined at rest or during maximal exercise. During submaximal exertion, at ~50% O₂ saturation of hemoglobin in the mixed venous blood, partial pressure of O₂ in individual horses was 2.5–4 Torr less in the NaHCO₃ treatment (vs. placebo). However, during maximal exercise, at ~9–12.5% O₂ saturation of hemoglobin in the mixed venous blood, the partial pressure of O₂ in the NaHCO₃-treated horses was 1.0–1.5 Torr less than in the placebo treatment.

Arterial CO₂ tension. See Fig. 6. Preexercise values of arterial CO₂ tension increased (P < 0.05) following NaHCO₃ administration. Whereas submaximal exercise was attended by a reduction in arterial CO₂ tension, hypercapnia of a similar magnitude developed during maximal exercise in both treatments. At 120 s of maximal exertion in the placebo and the NaHCO₃ experiments, arterial CO₂ tension had reached 55.4 ± 1.9 and 56.8 ± 1.6 Torr, respectively. During recovery from high-intensity exercise, a dramatic hyperventilation ensued in both treatments, as demonstrated by the large reduction in arterial CO₂ tension.

Arterial and mixed venous blood O₂ contents. See Fig. 7. Hemodilution in the NaHCO₃ experiments (Fig. 3B) caused the preexercise arterial and mixed venous blood O₂ contents (16.0 ± 0.4 and 11.5 ± 0.4 ml O₂/dl blood, respectively) to be less than corresponding values in the placebo study (P < 0.01), but the arterial-to-mixed venous blood O₂ content gradient remained unaffected.

0.04 and 3.3 ± 0.04°C in the placebo and NaHCO₃ experiments, respectively.

Arterial O₂ tension and hemoglobin-O₂ saturation. See Fig. 5. Preexercise data for these variables were similar in the placebo and NaHCO₃ treatments, and, during exercise performed at 6 and 8 m/s, arterial O₂ tension and hemoglobin-O₂ saturation were well maintained.

Maximal exercise was attended by a marked reduction of a similar magnitude in arterial O₂ tension in both treatments (Fig. 5A). As exercise duration progressed from 30 to 120 s, arterial O₂ tension did not change significantly in either treatment. At 120 s of maximal exercise in the placebo and NaHCO₃ experiments, the arterial O₂ tension was 72.4 ± 2.0 and 69.3 ± 1.8 Torr, respectively (vs. 101.5 ± 0.8 and 99.7 ± 1.1 Torr preexercise, respectively; both P < 0.0001).

Fig. 1. Arterial pH increased markedly following intravenous (IV) administration of NaHCO₃ to standing horses. A: whereas arterial pH did not change with submaximal exercise in either treatment, acidosis developed during maximal exertion. B: however, the higher plasma bicarbonate concentration in the NaHCO₃-treated horses allowed arterial pH to remain higher than in the placebo study during exercise. Rest #1, baseline measurements made before IV administration of placebo or NaHCO₃. Values are means ± SE. *Statistically significant difference from corresponding values in the placebo study, P < 0.001. #Statistically significant difference from immediately preceding data in the same treatment, P < 0.01. $Statistically significant difference from data for rest #1, preexercise, and submaximal exercise performed at 6 and 8 m/s in the same study, P < 0.01.

Fig. 2. Exercise-induced increment in blood lactate concentration was found to be similar in the placebo and NaHCO₃ treatments. Values are means ± SE. *Statistically significant difference from rest #1 as well as preexercise values in the same treatment, P < 0.0001. $Statistically significant difference from data for 8 m/s in the same treatment, P < 0.0001.
In both treatments, a significant ($P < 0.0001$) increment in arterial blood $O_2$ content was observed during exercise as hemoglobin concentration increased. However, because of the attenuated increment in hemoglobin concentration in the NaHCO$_3$-treated horses (Fig. 3B), the increment in arterial $O_2$ content was also attenuated ($P < 0.01$). At 120 s of maximal exertion, arterial blood $O_2$ content in the placebo and the NaHCO$_3$ treatments was $25.7 \pm 0.4$ and $24.5 \pm 0.3$ ml $O_2$/dl of blood, respectively ($P < 0.01$).

Work intensity-related changes in the mixed venous blood $O_2$ content, arterial-to-mixed venous blood $O_2$ content gradient, and $O_2$ extraction were observed in both treatments. However, the arterial-to-mixed venous blood $O_2$ content gradient of exercising horses in the NaHCO$_3$ experiments remained less than corresponding values in the placebo study ($P < 0.01$). At 120 s of maximal exercise, the arterial-to-mixed venous blood $O_2$ content gradient in the placebo and NaHCO$_3$ experiments was $23.3 \pm 0.4$ and $22.2 \pm 0.3$ ml $O_2$/dl of blood, respectively.

*Airway endoscopy.* All horses were observed to have experienced EIPH in both treatments.

**DISCUSSION**

Our observations in the placebo study regarding arterial hypoxemia, desaturation of hemoglobin, hypercapnia, acidosis, hyperthermia, increased plasma protein and hemoglobin concentrations, as well as increased $O_2$ extraction in horses performing short-term, high-intensity exercise (Figs. 1–7) mirrored data reported previously (23–27). Our primary objective in this study was to examine whether preexercise NaHCO$_3$ administration exaggerates the exercise-induced arterial hypoxemia as reported by Lloyd et al. (20) and thereby adversely affects the arterial hemoglobin-$O_2$ saturation and $O_2$ content in Thoroughbred horses performing strenuous exercise. In this context, the major findings of the present study were as follows. 1) Preexercise IV NaHCO$_3$ administration did not affect the arterial $O_2$ tension in healthy Thoroughbreds at rest, during submaximal exercise, or during short-term, high-intensity exercise (Fig. 5A), which elicited maximal heart rate and caused stress failure of pulmonary capillaries resulting in EIPH. Thus preexercise induction of metabolic alkalosis (Fig. 1) did not affect the development and/or severity of arterial hypoxemia in maximally exercising Thoroughbreds. Although these findings conflict with those of Lloyd et al. in horses premedicated with NaHCO$_3$, they are in agreement with data in human subjects (28) that preexercise NaHCO$_3$ administration does not affect arterial $O_2$ tension during exertion. 2) In agreement with data in human subjects (28), we also observed an attenuation of the desaturation of arterial hemoglobin during short-term, high-intensity exercise in Thoroughbreds premedicated with NaHCO$_3$ (Fig. 5B). 3) Despite these observations, however, the arterial blood $O_2$ content in the NaHCO$_3$ experiments decreased both preexercise as well as during exercise (Fig. 7). This was a consequence of the hemodilution that
ensued following IV NaHCO₃ infusion (Fig. 3). A) An attenuation of the exercise-induced expansion of the arterial-to-mixed venous blood O₂ content gradient occurred in the NaHCO₃ experiments (Fig. 7).

In agreement with previous work (23–27), we observed in both treatments that arterial hypoxemia was well developed, even at 30 s of maximal exertion, and that further significant changes in arterial O₂ tension did not occur as exercise duration progressed to 120 s (Fig. 5). Recently, it was suggested that pulmonary injury (i.e., capillary stress failure)-induced airway inflammatory mediator release plays a role in bringing about the exercise-induced arterial hypoxemia (30, 31). All horses in the present study had experienced EIPH in both treatments, indicating that pulmonary capillary stress failure had occurred (39).

According to the pulmonary injury-evoked airway inflammatory mediator release hypothesis (30, 31), an exaggeration of the arterial hypoxemia would be expected to occur with increasing exercise duration as structural changes in the blood-gas barrier (32, 39) intensify over time. Although this hypothesis has considerable appeal, the findings of Wetter et al. (40, 41) in exercising human subjects did not lend credence to it. Similarly, pretreatment of Thoroughbred horses with dexamethasone (to suppress the airway inflammatory response) and with a potent antihistaminic agent (H₁-receptor antagonist,tripelennamine HCl, to mitigate the effects of airway inflammatory and mast cell-released histamine on pulmonary capillary permeability) also did not support the pulmonary injury hypothesis for exercise-induced arterial hypoxemia in racehorses (26, 27). Furthermore, blood-gas studies during a repeat bout of strenuous exercise performed soon after the first exercise bout have also discounted the importance of structural changes in the blood-gas barrier (32, 39) in bringing about the exercise-induced arterial hypoxemia in human subjects as well as horses (4, 11, 23, 34). Among the causes of exercise-induced arterial hypoxemia in racehorses are the diffusion limitation to transfer of O₂ in the lungs (due to a significantly shortened pulmonary capillary transit time), the so-called relative alveolar hypventilation [as indicated by the
Fig. 7. A: following IV NaHCO₃ administration, the lower hemoglobin concentration (Fig. 3) caused preexercise arterial blood O₂ content (CaO₂) to decrease. This was accompanied by a reduction in the mixed venous blood O₂ content (CvO₂). During exercise, the increments in CaO₂ of the NaHCO₃-treated horses were attenuated as well. B: despite the above changes in CaO₂ and CvO₂ in the NaHCO₃-treated horses, preexercise CaO₂-to-CvO₂ gradient was unaffected. However, significant differences between treatments were observed during exercise. Values are means ± SE. *Statistically significant difference from corresponding values in the placebo study, P < 0.01. tStatistically significant difference from immediately preceding data in the same treatment, P < 0.01. tStatistically significant difference from rest #1, preexercise data, and data for exercise at 8 m/s in the same treatment, P < 0.01. tStatistically significant difference from 60 s of galloping in the same treatment, P < 0.01.

exercise-induced arterial hypercapnia (Fig. 6), despite significantly increased alveolar ventilation, and the ventilation-perfusion inequality (5, 19, 37). The contribution of relative alveolar hypoventilation to exercise-induced arterial hypoxemia would have been similar in our placebo and the NaHCO₃ treatments, as indicated by the similarity of arterial CO₂ tension during maximal exercise (Fig. 6). Although NaHCO₃ administration caused CO₂ retention in standing horses, arterial CO₂ tension during maximal exercise was not different from values in the placebo study. It is known that, despite synchronization of respiratory and stride frequencies in galloping horses, minute ventilation is not mechanically limited, as significant increments in tidal volume have been demonstrated on increasing treadmill slope at constant speed (3) and with a reduction in inspired O₂ concentration (29). This may account for the similarity of arterial CO₂ tension in exercising horses in the placebo and the NaHCO₃ treatments (Fig. 6).

Although in agreement with previous work (23–27), desaturation of arterial hemoglobin was observed during maximal exertion in both treatments (which intensified as exercise duration progressed to 120 s); an important finding in the present study was the significant attenuation of the desaturation of arterial hemoglobin in the NaHCO₃ experiments (Fig. 5B). Because arterial O₂ tension had not changed significantly in going from 30 to 120 s of maximal exercise in either treatment, it is likely that the intensification of the desaturation of arterial hemoglobin with increasing exercise duration was caused by the progressive rightward shift of the hemoglobin-O₂ dissociation curve as hyperthermia (Fig. 4), acidosis (Fig. 1), and hypercapnia (Fig. 6) intensified over time. Although the extent of exercise-induced hyperthermia, acidosis, and arterial hypercapnia was similar in the two treatments, the fact is that arterial pH of the exercising horses in the NaHCO₃ experiments was maintained at a significantly higher value (Fig. 1). The higher arterial pH of NaHCO₃-treated horses during galloping at 14 m/s on a 3.5% uphill grade likely contributed to the observed attenuation of the desaturation of arterial hemoglobin by limiting the extent of rightward shift of the hemoglobin-O₂ dissociation curve. Despite these findings, the fact is that the arterial blood O₂ content of exercising horses in the NaHCO₃ treatment was significantly less than that in the placebo study (Fig. 7). This was because of the significant hemodilution that ensued following IV administration of NaHCO₃ (Fig. 3). Erythrocyte 2,3-diphosphoglycerate is another factor known to influence the position of the hemoglobin-O₂ dissociation curve; however, differences in this variable between the placebo vs. NaHCO₃ treatments were not examined in the present study.

In the NaHCO₃-treated horses, a significant expansion of the plasma volume was demonstrated by the markedly diminished concentrations of plasma protein and hemoglobin (2, 7, 25), both preexercise as well as during exercise (Fig. 3). Although the hemodilution caused on NaHCO₃ administration did not significantly affect the arterial-to-mixed venous blood O₂ content gradient in standing horses, a significant (P < 0.01) attenuation of the exercise-induced expansion of the arterial-to-mixed venous blood O₂ content gradient was observed (Fig. 7). Whole body O₂ consumption is the product of cardiac output and arterial-to-mixed venous blood O₂ content gradient (Fick principle). Thus, because NaHCO₃ administration does not affect V̇O₂max (8, 20, 21, 28), it follows that the smaller arterial-to-mixed venous blood O₂ content gradient of maximally exercising horses in the NaHCO₃ experiments (Fig. 7) would have been augmented by an augmented cardiac output. Preexercise hypervolemia-induced further significant increase in cardiac output has been demonstrated in maximally exercising horses (13) and human subjects (14, 38). In maximally exercising horses, a 16% augmentation of cardiac output followed preexercise ~20% expansion of the plasma volume (13). This discussion regarding a further augmentation of cardiac output of maximally exercising horses in the NaHCO₃ treatment is relevant to the mechanism(s) for exercise-induced
arterial hypoxemia (Fig. 5) in that the largest contribution to exercise-induced arterial hypoxemia in racehorses is from the diffusion limitation to transfer of \( \text{O}_2 \) (37). The latter is probably related to the significant shortening of the transit time for blood in the pulmonary capillaries as cardiac output increases dramatically (5, 13, 19, 37). The scenario that maximally exercising horses in our NaHCO\(_3\) experiments may have had augmented cardiac output (13), in turn, suggests that there would have been a further truncation of the already shortened pulmonary capillary transit time during high-intensity exercise, which may have adversely affected the arterial \( \text{O}_2 \) tension. Although this was not found to be the case in the present study (Fig. 5), our findings are in agreement with previous studies in human athletes (38, 42) and in racehorses (25), wherein pre-exercise hyperventilation also failed to significantly affect the exercise-induced arterial hypoxemia. It is plausible that hyperventilation induced following NaHCO\(_3\) administration affected the pulmonary capillary blood volume and the distribution of ventilation-perfusion mismatching within the lungs, thereby affecting the pulmonary gas exchange of exercising horses.

Conflicting views have been presented regarding the ergogenic effects of preexercise NaHCO\(_3\) administration to racehorses (1, 6, 8–10, 12, 15, 17, 18, 20, 21, 33). In our experiments, neither were the investigators blinded as to the treatments nor was run time to fatigue determined; therefore, an assessment could not be made in this regard. However, based on our perception of the effort and encouragement required for individual horses to complete the 120 s of galloping at 14 m/s on a 3.5% uphill grade, it is opined that the placebo and NaHCO\(_3\) treatments were comparable.

In conclusion, our data demonstrated that preexercise IV administration of NaHCO\(_3\) to cause metabolic alkalosis in healthy Thoroughbred horses did not affect the development and/or severity of arterial hypoxemia during short-term, high-intensity exercise that elicited maximal heart rate and caused stress failure of pulmonary capillaries, resulting in EIPH. However, a significant attenuation of the desaturation of arterial hemoglobin was observed during maximal exercise in the NaHCO\(_3\)-treated horses, which had higher arterial pH. Despite these observations, the arterial blood \( \text{O}_2 \) content of exercising horses was found to be less in the NaHCO\(_3\) experiments because of the hemodilution, and a significant attenuation of the exercise-induced expansion of the arterial-to-mixed venous blood \( \text{O}_2 \) content gradient was observed.

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